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Gender-related differences in outcomes and attrition on antiretroviral treatment among an HIV-infected patient cohort in Zimbabwe: 2007–2010

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SUMMARY

Objectives: To determine (1) gender-related differences in antiretroviral therapy (ART) outcomes, and (2) gender-specific characteristics associated with attrition.
Methods: This was a retrospective patient record review of 3919 HIV-infected patients aged ≥15 years who initiated ART between 2007 and 2009 in 40 randomly selected ART facilities countrywide.
Results: Compared to females, males had more documented active tuberculosis (12% vs. 9%; $p < 0.02$) and a lower median CD4 cell count (117 cells/μl vs. 143 cells/μl; $p < 0.001$) at ART initiation. Males had a higher risk of attrition (adjusted hazard ratio (AHR) 1.28, 95% confidence interval (CI) 1.10–1.49) and mortality (AHR 1.56, 95% CI 1.10–2.20). Factors associated with attrition for both sexes were lower baseline weight (<45 kg and 45–60 kg vs. >60 kg), initiating ART at an urban health facility, and care at central/provincial or district/mission hospitals vs. primary healthcare facilities.
Conclusions: Our findings show that males presented late for ART initiation compared to females. Similar to other studies, males had higher patient attrition and mortality compared to females and this may be attributed in part to late presentation for HIV treatment and care. These observations highlight the need to encourage early HIV testing and enrolment into HIV treatment and care, and eventually patient retention on ART, particularly amongst men.

1. Introduction

With only 12% of the world's population, Sub-Saharan Africa has 68% of the world's burden of HIV/AIDS cases.[1] Zimbabwe, a country in southern Africa, is also badly affected by the HIV/AIDS epidemic, with recent statistics showing an HIV prevalence of 15% in the 15–49 years age group according to the 2010–2011 Zimbabwe Demographic and Health Survey.[2]

Since the national antiretroviral treatment (ART) programme was initiated in 2004, there has been a continuous increase in the cohort of HIV-infected individuals accessing this life-saving intervention in Zimbabwe. The number of health facilities offering ART services increased from 7 in 2004 to 960 by December 2012,[3] and those receiving ART increased from 24 500 people in 2005 to 531 136 by the end of 2012.[3] In terms of adult ART coverage, the country reached universal access levels of 85% in 2012, but with changing global guidelines, which recommended earlier ART initiation, the coverage dropped to 53% in December 2013.[4]

Despite this continued scale-up in numbers of HIV-infected patients receiving ART, a growing concern in most ART programmes is patient retention in care, which is critical for the success of such programmes. A meta-analysis of 32 ART programs in Africa, excluding Zimbabwe, showed that retention was 60%, with loss to follow-up being the major cause of attrition, followed by death.[5] Partly associated with attrition from HIV treatment and care is male gender,[6–11] and this has been attributed in part to

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advanced HIV disease at the time of ART initiation[7,12] and poor treatment adherence among males.[11,13] Despite knowing that attrition is higher among males, little is known about differences in the immunological response to ART between males and females in the routine ART programme setting. Furthermore, few studies have assessed the factors specific to males and females that influence attrition from ART. Identifying these gender-specific attrition-associated factors is critical for determining priority areas for improving patient retention for each sex.

In Zimbabwe, a review of the national ART programme revealed that patient retention rates at 36 months was 64.4% and that male gender increased the risk of attrition.[14] Using this dataset we conducted an extended data analysis aimed at determining: (1) gender-related differences in ART outcomes, primarily attrition from treatment, mortality, loss to follow-up, and immunological failure, and (2) gender-specific characteristics associated with attrition.

2. Methods

2.1. Study design

We conducted a retrospective cohort study using routinely collected ART programme data.

2.2. Setting: general and site-specific

2.2.1. Clinical procedures in the Zimbabwe National ART Programme

ART eligibility between 2007 and 2009 was based on national guidelines[15] adapted from the World Health Organization (WHO):[16] ART was initiated in patients with a documented HIV-positive test who were classified with WHO clinical stage 3 disease and a CD4+ cell count <350/μl, or WHO clinical stage 4 disease, or who had a CD4+ cell count <200/μl irrespective of the WHO staging. Although not mandatory, other recommended psychosocial criteria for evaluating ART eligibility, as they are considered a measure of patient reliability on treatment, were the following: (1) compliance with co-trimoxazole prophylaxis using pill counts or keeping appointments, as this will indicate the likelihood of adherence to ART; (2) completion of prescribed counselling session(s); (3) availability of a treatment partner and/or disclosure to that treatment partner; and (4) ease of follow-up of the patient. Co-trimoxazole was commenced at least 2 weeks before ART initiation among adult patients who were either in WHO clinical stage 2 or higher, or who had a CD4 cell count <200/μl; this would be continued indefinitely or until the CD4 count was >200/μl for >6 months.

Women were checked for pregnancy prior to ART initiation as it was deemed preferable to commence ART after the first trimester so as to minimize the risk of teratogenesis.[16] The recommended first-line ART regimen included two nucleoside reverse transcriptase inhibitors (NRTIs), namely stavudine and lamivudine, and one non-nucleoside reverse transcriptase inhibitor (NNRTI), namely nevirapine. Zidovudine could replace stavudine in the event of drug toxicity, while efavirenz could replace nevirapine in the event of an adverse reaction, during pregnancy, or if a patient was commenced on tuberculosis (TB) treatment.

2.2.2. Follow-up in the Zimbabwe National ART Programme

Patients are seen every 2 weeks during the first month of ART initiation, then every month for the following 3 months, and are reviewed every 3 months after the first 4 months. Patients can also visit the clinic immediately if they experience any side effects. Recommended clinical and laboratory monitoring indices include the patient's weight, WHO clinical stage, development of opportunistic infections (OIs), complete blood count (CBC), serum alanine transaminase (ALT), serum creatinine, and when available CD4+ cell counts. (Note: CD4 testing was not widely available between 2007 and 2009. By end of 2009, 68 CD4 machines were in 59 facilities located in 47 out of the country's 62 districts.[17]) Routine clinical monitoring is recommended every 3 months, CBC and CD4 cell counts should be conducted every 6 months, and ALT and creatinine should be measured every 12 months. Patient demographic, clinical, and laboratory information and visit dates are recorded in the Ministry of Health and Child Care (MOHCC) medical records maintained at the health facility.

2.2.3. Treatment outcome measures

ART outcomes during data abstraction were categorized as alive and retained on therapy, died, stopped treatment, transferred out, defaulted, loss-to-follow-up (LTFU), and other. LTFU was defined as patient absenteeism from a healthcare facility for >90 days after the last scheduled appointment with the healthcare provider or pharmacy, whilst defaulters were those who had not come back to the clinic for <90 days from the last scheduled appointment. The LTFU date was recorded as the date of the most recent visit or one day after ART initiation if patients only attended the initiation visit. In this analysis, our primary outcomes of interest were clinical ART outcomes and immunological failure. Clinical outcomes comprised all-cause mortality, LTFU, and attrition. Attrition referred to patients who were documented as having stopped ART, died, or who were LTFU. Immunological failure was defined in line with WHO 2006[16] and the Zimbabwe National ART guidelines[15] as (1) a decline in CD4+ cell count after ≥6 months on therapy, (2) a fall to pre-therapy CD4 count/percentage, or (3) a CD4 count ≤100 cells/μl after at least 6 months on therapy. Overall immunological failure was then determined as having been classified with immunological failure by any of the three criteria stated above.

2.2.4. Study sites

The study was conducted in 40 of 70 health facilities that were providing ART services to ≥50 HIV-infected patients for ≥6 months by May 31, 2008, for the purposes of logistical and financial feasibility. All provinces countrywide were represented in the sample whereby sites were selected randomly with the probability of selection being proportional to the number of adult patients who had received ART at each site, by May 31, 2008.

2.3. Study participants

Patients were included in the study if they were HIV-infected and ≥15 years old and had initiated ART between January 1, 2007 and December 31, 2009. Transfer-in patients were excluded from the sampling frame in order to avoid double-counting, as they may have been abstracted as transfer-out at another selected study site. A minimum of 3842 patients were required for the study, assuming a design effect of 2, 50% of adult patients were retained on ART at 12 months after ART initiation, a 95% confidence interval of ±2.5%, and 20% of charts were missing. Patient charts were selected randomly at each site using an R program.

2.4. Data variables, source of data, and data collection

Data variables included demographic data such as sex and age at enrolment into HIV care. Clinical information abstracted included WHO stage, weight, co-trimoxazole use, and CD4 count prior to ART initiation. Follow-up visit information included weight, haemoglobin, CD4 count, clinical stage, co-trimoxazole prescription, ART regimen, and the final patient outcome. Selected patient files were retrieved by ART clinic staff who were responsible for retrieving selected patient files, whilst missing ones were replaced by the next eligible patient record on the randomly ordered list. Trained health

Table 1
Baseline sociodemographic and clinical characteristics of the recruited HIV-positive cohort in the Zimbabwe National ART Programme (2007–2010)

Patient characteristics	*n*	*N*	Original dataset[a]			Multiple imputation based data			*p*-Value[b]
			All patients (*N* = 3919)	Male (*n* = 1393)	Female (*n* = 2514)	All patients (*N* = 3919)	Male (*n* = 1393)	Female (*n* = 2514)	
			Percentage (95% CI) or median (IQR)	Percentage (95% CI) or median (IQR)	Percentage (95% CI) or median (IQR)	Percentage (95% CI) or median (IQR)	Percentage (95% CI) or median (IQR)	Percentage (95% CI) or median (IQR)	
Sociodemographics									
Age, years	3733	3733	37 (32–45)	39 (34–48)	36 (31–44)	37 (32–45)	39 (34–48)	36 (31–44)	<0.001
Age group, years									
15–29	597	3733	16.5% (14.4–18.5)	10.8% (8.3–13.4)	19.5% (17.2–21.8)	16.5% (14.5–18.5)	11.0% (8.6–13.5)	19.6% (17.3–21.8)	<0.001
30–39	1548	3733	41.7% (40.0–43.5)	40.1% (37.4–42.8)	42.6% (40.5–44.6)	41.4% (39.6–43.2)	39.8% (37.0–42.5)	42.3% (40.2–44.4)	
40–49	991	3733	26.3% (24.8–27.8)	28.8% (26.7–30.8)	25.0% (23.4–26.6)	26.5% (24.9–28.1)	28.9% (26.7–31.1)	25.2% (23.6–26.8)	
50 and above	597	3733	15.5% (14.3–16.8)	20.2% (17.5–23.0)	13.0% (12.0–14.0)	15.6% (14.3–16.8)	20.3% (17.5–23.1)	12.9% (11.9–14.0)	
Missing	186	3919	4.8%	4.2%	5.0%	-	-	-	
Weight, kg	2870	2870	55 (49–61)	56.8 (51–63)	53.7 (47.6–60.0)	55.0 (48.4–61.4)	56.9(47–60)	53.9(47–60)	<0.001
Weight category, kg									
<45	369	2870	13.1% (10.3–16.0)	8.2% (5.4–11.1)	15.6% (12.3–19.0)	13.3% (10.8–15.8)	8.9% (6.4–11.4)	16.1% (13.2–19.0)	<0.001
45–60	1 722	2870	60.4% (57.9–62.3)	54.1% (49.8–58.3)	56.7% (53.7–59.7)	60.0% (57.6–62.3)	53.0% (48.7–57.3)	56.1% (53.3–58.9)	
60+	779	2870	26.5% (22.9–30.1)	37.7% (32.8–42.6)	27.7% (23.6–31.7)	26.8% (23.5–30.0)	38.1% (33.4–42.8)	27.7% (24.2–31.3)	
Missing	1049	3919	26.8%	26.6%	26.8%	-	-	-	
Clinical characteristics									
Days from HIV care start to ART initiation	2927	2927	29 (2–126)	29 (2–113)	30 (2–131)	36 (1–165)	35 (1–155)	37 (1–173)	0.303
Duration on observed ART (in months)	3919	3919	16.4 (8.2–27.1)	15.5 (6.4–26.0)	16.8 (9.2–27.6)	16.4 (8.2–27.1)	15.5 (6.4–26.2)	16.8 (9.2–27.6)	0.018
WHO clinical stage									
1/2	390	3289	12.4% (6.8–18.1)	11.7% (6.2–17.1)	12.9% (6.8–19.0)	14.4% (8.6–20.1)	11.8% (7.2–16.4)	13.0% (7.9–18.2)	0.1015
3	2413	3289	73.5% (66.9–80.1)	71.9% (65.3–78.6)	74.3% (67.2–81.4)	70.5% (63.9–77.1)	71.9% (66.2–77.6)	74.0% (68.0–80.0)	
4	486	3289	14.1% (9.7–18.4)	16.4% (11.6–21.1)	12.8% (8.3–17.3)	15.1% (11.4–19.0)	16.3% (12.2–20.3)	13.0% (9.2–16.8)	
Missing	630	3919	16.1%	16.3%	15.8%	-	-	-	
Active TB[c]									
Yes	268	2231	12.0% (9.0–15.0)	14.6% (91.8–20.0)	10.4% (8.3–12.6)	10.3% (7.9–12.6)	12.3% (8.4–16.2)	9.1% (7.1–11.2)	0.020
No	1963	2231	88.0% (85.0–91.0)	85.4% (80.0–90.8)	89.6% (87.4–91.7)	89.7% (87.4–92.1)	87.7% (83.8–91.6)	90.9% (88.8–92.9)	
Missing	1688	3919	43.1%	42.3%	43.6%	-	-	-	
Documented prior TB[c]									
Yes	408	3919	10.3% (5.2–15.3)	12.9% (6.4–19.5)	8.6% (3.9–13.3)	10.3% (6.5–19.5)	13.0% (6.5–19.5)	8.7% (4.0–13.4)	0.005
No	3511	3919	89.7% (84.7–94.8)	87.1% (80.5–93.6)	91.4% (86.7–96.1)	89.7% (84.7–94.8)	87.0% (80.5–93.5)	91.3% (86.6–96.0)	
Haemoglobin, g/dl	898	898	10.8 (9.6–12.1)	11.3 (9.9–12.8)	10.7 (9.5–11.8)	10.8 (9.2–12.4)	11.3 (9.7–12.9)	10.6 (9.1–12.1)	0.001
Anaemia[d]									
Yes	695	898	77.4% (74.5–80.0)	76.3% (71.2–80.6)	78.0% (74.4–81.2)	78.6% (76.0–81.2)	80.6% (76.0–85.2)	77.5% (74.1–80.8)	0.023
No	203	898	22.6% (20.0–25.5)	23.7% (19.4–28.8)	22.0% (18.8–25.6)	21.4% (18.8–24.0)	19.4% (14.8–24.0)	22.5% (19.2–25.9)	
Missing	3021	3919	77.1%	77.3%	76.9%	-	-	-	
CD4 count, cells/ml	1834	3919	121 (55–194)	104 (48–183)	127 (61–199)	121 (55–194)	104 (48–183)	127 (60–199)	<0.001
CD4 count category, cells/ml									
<50	401	1834	22.4% (20.2–24.6)	26.3% (23.2–29.4)	19.9% (17.6–22.1)	22.4% (19.8–25.1)	27.0% (23.7–30.3)	20.3% (18.0–22.6)	<0.001
50–200	1031	1834	54.9% (51.2–58.7)	55.3% (51.8–58.9)	56.2% (51.3–61.1)	53.4% (49.8–57.1)	54.9% (51.4–58.4)	55.9% (52.6–59.1)	
≥200	402	1834	22.7% (19.5–25.9)	18.3% (16.0–20.6)	24.0% (19.6–28.4)	24.1% (19.6–28.6)	18.1% (15.3–20.9)	23.8% (20.6–27.1)	
Missing	2085	3919	53.2%	51.7%	54.1%	-	-	-	
Level of healthcare									
Primary healthcare facility	588	3919	15.0% (13.9–16.2)	17.9% (15.9–20.0)	13.4% (12.1–14.8)	9.4% (3.9–14.9)	11.0% (4.6–17.4)	8.6% (3.3–13.8)	0.169
District/mission hospital	2451	3919	62.5% (61.0–64.0)	59.2% (56.6–61.8)	64.5% (62.6–66.4)	61.5% (36.8–86.2)	59.5% (34.2–84.7)	62.7% (38.2–87.1)	
Central/provincial hospital	880	3919	22.5% (21.2–23.8)	22.9% (20.8–25.2)	22.1% (20.5–23.7)	29.0% (5.0–53.1)	29.0% (4.9–54.1)	28.8% (4.9–52.7)	

Site type								
Rural	1975	3919	46.7% (22.0–71.3)	44.6% (19.7–69.6)	48.0% (23.5–72.6)	46.7% (22.0–71.4)	44.5% (19.5–69.6)	47.9% (23.3–72.5)	0.078
Urban	1944	3919	53.3% (28.7–78.0)	55.4% (30.4–80.3)	52.0% (27.4–76.5)	53.3% (28.6–78.0)	55.5% (30.4–80.5)	52.1% (27.5–76.7)	
OI/ART clinic site size[e]									
50–999	1699	3919	27.4% (27.4–27.4)	26.1% (23.7–28.6)	28.1% (26.8–29.5)	27.4% (27.4–27.4)	26.1% (23.7–28.5)	28.1% (26.8–29.5)	0.289
1000+	2220	3919	72.6% (72.6–72.6)	73.9% (71.4–76.3)	71.9% (70.5–73.2)	72.6% (72.6–72.6)	73.9% (71.5–76.3)	71.9% (70.5–73.2)	

ART, antiretroviral therapy; CI, confidence interval; IQR, interquartile range; WHO, World Health Organization; TB, tuberculosis; OI, opportunistic infection; *n* = number of patients in each category of a variable; *N* = total number of patients with recorded data for each variable.

[a] Sex was missing for 12 patients.

[b] All statistical comparisons were performed on imputed data. Logistic regression was used for categorical variables (e.g., age group, weight category, etc.); gender was regressed on the categorical variable of interest. Linear regression was used for continuous variables (e.g., age in years, weight in kg, etc.); the continuous variable of interest was regressed on gender. Square root transformations were used for continuous duration variables.

[c] TB is defined as either pulmonary TB or extrapulmonary TB.

[d] Anaemia is defined as follows: males ≥15 years with haemoglobin level <13 g/dl; non-pregnant women with haemoglobin levels <12 g/dl; pregnant women with haemoglobin levels <11 g/dl.

[e] OI/ART clinic site size refers to the number of patients enrolled on ART at an opportunistic infections/antiretroviral therapy clinic as at December 31, 2009.

workers were responsible for abstracting information from patient files into paper-based questionnaires, which were eventually entered into an MS Access database and scanned separately into a TeleForm database. Differences in the two databases were identified using the SAS %COMPARWS Macro.[18]

2.5. Statistical analysis

Data management was done using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), whilst all statistical analyses were performed using Stata/IC 12.1 (StataCorp, 2011, Stata Statistical Software: Release 12.1; StataCorp LP, College Station, TX, USA). Data were weighted and the analysis accounted for the complex design of the survey using the 'svy' prefix command in Stata. Domain analyses were performed using the 'subpop()' option.

Missing data were assumed 'missing at random' (MAR)[19] and were multiple imputed by chained equations using the 'mi impute chained' procedure in Stata. Twenty imputed datasets were created and estimates were combined according to Rubin's rules[19] using the 'mi estimate' procedure. The imputation model included the Nelson–Aelen estimate of cumulative hazard,[20] baseline demographic and clinical variables, and the event indicator. Time-to-event data were complete for all individuals. Twenty-five patients were LTFU after their first clinic visit and were assigned one day of person-time.

Gender differences in baseline clinical and demographic characteristics were analysed using linear and logistic regression models. These analyses were limited to the first imputed dataset. Cox proportional hazards models were used to compare differences in ART outcomes (mortality, LTFU, and attrition) and immunological ART outcomes by gender, and also to identify gender-specific factors associated with attrition. Multivariable adjusted hazard ratios (HRs), their 95% confidence intervals (CI), and *p*-values were calculated whilst adjusting for the potential confounding effects of age, baseline weight, baseline CD4 count, baseline WHO staging, prior/current TB, anaemia, size and location of OI/ART clinic, and level of health facility. Incidence rates were also calculated for all clinical ART outcomes and immunological failure, with the incidence rate being defined as the number of new cases attaining each outcome in the patient population per 100 person-years (PY) at risk.

For time-to-event analyses, patients who transferred to another clinic were censored at the date of transfer. However, for estimating the various immunological ART outcome proportions, the analysis was restricted to those patients with a baseline CD4 count and at least one CD4 count result 6 months after ART initiation. Baseline CD4 count was defined as the value on the date closest to ART start date but not more than 182 days prior to that date or more than 1 day after that date.

2.6. Ethics and approval

The study protocol was approved by the Medical Research Council of Zimbabwe (MRCZ) and the Institutional Review Board (IRB) of the United States Centers for Disease Control and Prevention prior to data collection. The Union Ethics Advisory Group also reviewed and approved this extended analysis protocol.

3. Results

3.1. Baseline demographic, clinical, and immunological characteristics

Data were abstracted from 3919 medical charts of patients eligible for ART. The level of missing baseline patient data in these charts varied from <1% (*n* = 12) for sex, 5% (*n* = 186) for age,

16% (n = 630) for WHO stage, 27% (n = 1049) for body weight, 43% (n = 1688) for current active TB, and 53% (n = 2085) for CD4 cell count to 77% (n = 3031) for haemoglobin levels. Original and imputed datasets are reported in Table 1, for overall and gender-specific baseline demographic and clinical characteristics. The results of the weighted imputed data are reported below.

At enrolment into HIV treatment, men were older (39 (interquartile range (IQR) 34–48) vs. 36 (IQR 31–44) years; $p < 0.001$), had higher median baseline weight (57 (IQR 47–60) vs. 54 (IQR 47–60) kg; $p < 0.001$), and were more likely to have documented current active TB disease (12% vs. 9%; $p = 0.02$) and documented prior TB disease (13% vs. 9%; $p = 0.005$). Although no gender differences were noted for the period between enrolment into HIV care and ART initiation, men were retained on treatment for fewer months when compared to women (156 (IQR 6–26) months vs. 17 (IQR 9–28) months; $p = 0.018$). Similarly the median baseline CD4 cell count among males was lower when compared to females (104 cells/μl (IQR 48–183) vs. 127 cells/μl (IQR 105–181); $p < 0.001$) and a greater proportion of men compared to women had a baseline CD4 count <50 cells/μl (27% vs. 20%, $p < 0.001$). The prevalence of anaemia was high at 79% of the 23% with recorded baseline haemoglobin levels, and anaemia prevalence was higher among men than women (81% vs. 78%; $p = 0.023$).

3.2. Comparison of patient outcomes by gender

Table 2 shows comparisons of clinical and immunological ART outcomes by gender. Males had a higher incidence of attrition (24.0 vs. 19.3 cases/100 PY; $p < 0.003$), a higher incidence of mortality (4.7 vs. 2.9 deaths/100 PY; $p = 0.003$), and a higher LTFU (4.7 vs. 2.9 cases/100 PY; $p = 0.027$). Males continued to have a higher risk of attrition (adjusted hazard ratio (AHR) 1.24, 95% confidence interval (CI) 1.08–1.43; $p = 0.004$), mortality (AHR 1.56, 95% CI 1.10–2.20; $p = 0.014$), and LTFU (AHR 1.23, 95% CI 1.05–1.44; $p = 0.012$) after adjusting for potential confounding. The overall incidence of clinical immunological failure was low in this cohort at 0.3 cases/100 PY and there were no significant differences when stratified by gender (AHR 1.24, 95% CI 0.25–6.18; $p = 0.786$) after adjusting for potential confounders.

3.3. Gender-related differences associated with attrition

Table 3 shows gender-specific factors associated with attrition. For males, those with baseline weights of 45–60 kg (AHR 1.37, 95% CI 1.06–1.76; $p = 0.017$) and <45 kg (AHR 1.82, 95% CI 1.18–2.81; $p = 0.009$) were at increased risk of attrition when compared to those with baseline weights ≥60 kg. Among females, only those with baseline weight <45 kg (AHR 1.92, 95% CI 1.36–2.73; $p = 0.001$) were at increased risk of attrition compared to those ≥60 kg. There was a higher risk of attrition among males with WHO stage 4 compared to those with WHO stage 1 or 2 (AHR 1.87, 95% CI 1.28–2.73; $p = 0.003$), whilst no differences were noted among females. Accessing treatment from urban areas in comparison to rural areas was associated with a higher risk of attrition from care for both males (AHR 2.48, 95% CI 1.06–5.81; $p = 0.0037$) and females (AHR 3.12, 95% CI 1.29–7.51; $p = 0.013$).

The baseline CD4 count, current active TB, and prior TB infection were not significant risk factors for attrition in either males or females after adjusting for confounding. However, attrition was higher for males accessing ART from district/mission hospitals (AHR 4.47, 95% CI 1.36–14.67; $p = 0.015$) or central/provincial hospitals (AHR 3.52, 95% CI 1.12–11.11; $p = 0.033$) when compared to those accessing treatment from primary healthcare facilities. A similar trend was observed for females receiving treatment from district/mission hospitals (AHR 7.37, 95% CI 2.32–23.36; $p = 0.001$) and central/provincial hospitals (AHR 4.74, 95% CI 1.55–14.53; $p = 0.008$).

Table 2
Comparison of clinical and immunological ART outcomes by gender[a]

	Original	Multiple imputation (N = 3 919)						
	Frequency (N = 3 919)	All patients[b]	Males (n = 1 393)	Females (n = 2514)	Bivariate		Multivariable[c]	
		Rate/100 PY[d]	Rate/100 PY	Rate/100 PY	HR (95% CI)	p-Value	AHR (95% CI)	p -Value
ART outcomes								
Attrition[e]	1149	20.9	24.0	19.3	**1.22 (1.07–1.39)**	**0.003**	**1.24 (1.08–1.43)**	**0.004**
Mortality	221	3.5	4.7	2.9	**1.55 (1.23–2.14)**	**0.009**	**1.56 (1.10–2.20)**	**0.014**
Loss to follow-up	921	16.9	18.7	15.9	**1.16 (1.02–1.33)**	**0.027**	**1.23 (1.05–1.44)**	**0.012**
Stopped ART	7	0.1	0.2	0.1	1.34 (0.52–3.51)	0.536	-	-
Immunological failure by different definitions								
CD4 count <100 cells/ml after at least 6 months of initiating therapy	2 199	1.6	1.9	1.4	1.40 (0.95–2.05)	0.084	1.02 (0.67–1.55)	0.925
CD4 count less than pre-therapy CD4 count at baseline after at least 6 months of initiating therapy	981	2.0	2.5	1.8	1.38 (0.93–2.03)	0.102	1.17 (0.70–1.94)	0.539
50% drop from peak CD4 count value	461	1.7	1.5	1.7	0.89 (0.24–3.34)	0.855	0.85 (0.21–3.42)	0.802
Immunological failure (any definition)[f]	1979	0.3	0.3	0.2	1.37 (0.27–6.88)	0.694	1.24 (0.25–6.18)	0.786

ART = antiretroviral therapy; PY = person years; HR = hazard ratio; AHR = adjusted hazard ratio; CI = confidence interval; TB = tuberculosis.
N = total number of patients with recorded data for each variable.
The bold font was meant to highlight all analysis which had significant p-values (i.e. $p < 0.05$).
[a] Females are the reference category when interpreting both the univariate and multivariate-adjusted hazard ratios.
[b] Take note that sex was missing for 12 patients.
[c] Hazard ratios have been adjusted for potential confounding effect of age, baseline weight, baseline WHO clinical stage, prior/current TB, anemia, patient residence and size of OI/ART clinic.
[d] Rate/100PY is defined as as the number of new cases attaining each outcome in the patient population per 100 person-years at risk.
[e] Attrition refers to patients who were documented as having died, stopped ART or were lost to follow-up (a patient absent from a healthcare facility for more than 90 days after his/her last scheduled appointment with the health care provider or pharmacy).
[f] Immunologic failure is defined as either CD4<100cells/ml 6 months after initiating therapy; CD4 count less than pre-therapy CD4 count,at least 6 months after initiating ART; a 50% drop from the peak CD4 cell count value; or any other definition of immunologic failure.

Table 3
Gender-specific ART attrition in relation to baseline clinical and sociodemographic characteristics among an HIV-positive cohort in the Zimbabwe National ART Programme (2007–2010)

Patient characteristics ($N = 3919$)[a]	Attrition[b]							
	Males ($n = 1393$)				Females ($n = 2514$)			
	HR (95% CI)	*p*-Value	AHR (95% CI)[c]	*p*-Value	HR (95% CI)	*p*-Value	AHR (95% CI)[c]	*p*-Value
Socio-demographics								
Age group, years								
15–29	Reference		Reference		Reference		Reference	
30–39	0.92 (0.66–1.28)	0.599	0.98 (0.66–1.46)	0.920	0.88 (0.74–1.04)	0.119	0.91 (0.77–1.08)	0.277
40–49	0.78 (0.55–1.12)	0.175	0.86 (0.55–1.34)	0.485	0.71 (0.53–0.96)	0.029	0.72 (0.51–1.02)	0.064
50 and above	0.80 (0.61–1.04)	0.090	0.96 (0.69–1.34)	0.805	0.66 (0.45–0.96)	0.033	0.70 (0.45–1.08)	0.100
Weight category, kg								
60+	Reference		Reference		Reference		Reference	
45–60	**1.39 (1.08–1.79)**	**0.012**	**1.37 (1.06–1.76)**	**0.017**	1.20 (0.96–1.50)	0.105	1.15 (0.91–1.46)	0.237
<45	**2.06 (1.44–2.94)**	**<0.001**	**1.82 (1.18–2.81)**	**0.009**	**2.02 (1.44–2.83)**	**<0.001**	**1.92 (1.36–2.73)**	**0.001**
Clinical characteristics								
WHO clinical stage, %								
1–2	Reference		Reference		Reference		Reference	
3	1.47 (0.93–2.34)	0.098	1.29 (0.89–1.88)	0.174	1.12 (0.74–1.70)	0.590	1.05 (0.66–1.67)	0.832
4	**1.95 (1.29–2.94)**	**0.003**	**1.87 (1.28–2.73)**	**0.003**	**1.64 (1.03–2.58)**	**0.036**	1.54 (0.88–2.67)	0.123
Active TB (PTB or EPTB), %								
No	Reference		Reference		Reference		Reference	
Yes	0.71 (0.46–1.10)	0.119	0.80 (0.53–1.23)	0.289	0.91 (0.61–1.35)	0.615	0.95 (0.67–1.34)	0.759
Prior TB (PTB or EPTB), %								
No	Reference		Reference		Reference		Reference	
Yes	0.82 (0.50–1.35)	0.431	0.84 (0.49–1.45)	0.521	0.91 (0.60–1.38)	0.647	0.85 (0.64–1.13)	0.254
CD4 count category, cells/ml								
≥200	Reference		Reference		Reference		Reference	
50–200	1.03 (0.70–1.52)	0.870	0.99 (0.70–1.41)	0. 960	1.07 (0.79–1.43)	0.652	0.97 (0.75–1.27)	0.831
<50	1.39 (0.96–2.00)	0.081	1.25 (0.87–1.80)	0.206	1.64 (1.13–2.37)	0.014	1.39 (0.95–2.03)	0.085
Level of healthcare								
Primary healthcare facility	Reference		Reference		Reference		Reference	
District/mission hospital	2.67 (0.89–8.04)	0.078	4.47 (1.36–14.67)	0.015	3.10 (1.29–7.47)	0.013	7.37 (2.32–23.36)	0.001
Central/provincial hospital	3.51 (1.25–9.83)	0.018	3.52 (1.12–11.11)	0.033	3.85 (1.69–8.76)	0.002	4.74 (1.55–14.53)	0.008
Site type								
Rural	Reference		Reference		Reference		Reference	
Urban	1.74 (1.02–2.98)	0.043	2.48 (1.06–5.81)	0.037	1.73 (0.94–3.20)	0.076	3.12 (1.29–7.51)	0.013
OI/ART clinic site size[d]								
50–999	Reference		Reference		Reference		Reference	
1000+	1.70 (0.95–3.02)	0.072	0.87 (0.50–1.52)	0.618	1.51 (0.81–2.81)	0.186	0.81 (0.40–1.67)	0.565

ART, antiretroviral therapy; HR, hazard ratio; CI, confidence interval; AHR, adjusted hazard ratio; WHO, World Health Organization; TB, tuberculosis; OI, opportunistic infection; PTB, pulmonary TB; EPTB, extrapulmonary TB; N = total number of patients with recorded data for each variable.
The bold font was meant to highlight all analysis which had significant *p*-values (i.e. $p < 0.05$).

[a] Sex is missing for 12 patients.

[b] Attrition refers to patients who were documented as having died, stopped ART, or were lost to follow-up (a patient absent from a healthcare facility for more than 90 days after his/her last scheduled appointment with the healthcare provider or pharmacy).

[c] Hazard ratios have been adjusted for potential confounding effects of age, baseline weight, baseline CD4 count, baseline WHO staging, prior/current TB, anaemia, patient residence, and size of OI/ART clinic.

[d] OI/ART clinic site size refers to the number of patients enrolled on ART at an opportunistic infections/antiretroviral therapy clinic as at December 31, 2009.

4. Discussion

This study highlights the differences in patient characteristics as well as treatment outcomes between males and females in a cohort of HIV-infected patients on ART in the Zimbabwe National ART Programme. In this study we observed that males had poorer clinical status prior to initiating ART with regards to current and previous TB illness when compared to females. Among the few patients who had haemoglobin measurements taken, anaemia was more prevalent among males than females, and anaemia has been shown to be a strong risk factor for disease progression and death independent of CD4 count and viral load.[21,22] Males also had lower CD4+ cell counts upon initiating ART when compared to females. These observations indicate that males generally present late for HIV treatment and care when compared to their female counterparts. This is similar to findings of other studies in both resource-limited settings[7,10,23] and well-resourced settings,[24–26] which have shown that males tend to have more advanced HIV disease upon initiation of ART. As shown in other studies, such differences in late ART initiation between males and females can be attributed in part to clinic-level factors such as the presence of prevention of mother-to-child transmission of HIV (PMTCT) services at ART sites[27,28] and patient-level factors such as pregnancy and entry into care through antenatal care (ANC) or PMTCT rather than through voluntary counselling and testing (VCT).[27] This may also be attributed to a notion of masculinity that portrays men as resilient and disease-free and hence contradicts expected health-seeking behaviours such as attending regular hospital visits, as reported in a local study among rural men.[29]

Similar to findings from other studies,[12,13,30] males had higher mortality and attrition from ART care in comparison to females. In our study, mortality was defined as that which had been documented in the ART registers and patient files upon abstraction of data. Since no efforts were made to follow-up these patients, it is highly likely that there may have been more deaths among those who were defined as LTFU in the attrition group, as was reported in one unpublished study in Zimbabwe (Chigu 2011) and in other studies from ART programmes in resource-limited settings.[31] Among males, factors that were associated with attrition were lower baseline weight, advanced WHO stage, and accessing treatment from urban areas. A study done within the South African ART programme also showed higher mortality among

males and also attributed this in part to more advanced disease at the time ART initiation and differences in response to treatment.[7]

Similar to males, attrition among females was also associated with lower baseline weight. Low weight is a common problem among HIV-infected patients even in the era of ART[32] and has also been shown to be a strong independent predictor of mortality.[33] Poor nutritional status in HIV-infected patients leads to low immunity, which predisposes these patients to many severe OIs, particularly TB. TB is highly prevalent in Sub-Saharan Africa and is not easily detected clinically; it is therefore likely to manifest in the early stages of immune reconstitution syndrome. Such TB is better detected using more sensitive techniques such as the Gene Xpert MTB/RIF assay,[34] which until recently was not available in Zimbabwe, compared to the conventional acid-fast bacilli smear microscopy. This could partly explain why only 12% of patients in this study had active TB at baseline in a setting with high HIV/TB co-infection.

There are two possible reasons for the higher risk of attrition among those accessing treatment from urban areas and higher level health facilities. Firstly, this may be explained by patients from rural areas or lower level health facilities initiating ART in urban or higher level health facilities where there was more chance of finding doctors; these doctors initiated ART and the patients then unofficially self-transferred out to rural clinics and lower level facilities as ART decentralization expanded. These patients may therefore have been misclassified as LTFU. In Zimbabwe, ART initiations were officially done only by medical doctors until recently; however nurses who predominantly run rural and lower level health facilities have since been empowered to start ART. In Uganda[35] and Malawi,[36] a considerable proportion of these LFTU patients were receiving ART at another facility upon tracing them. Secondly, higher proportions of patients with advanced disease may have attended these urban and higher level facilities for treatment and eventually ART initiation, as they are generally perceived to offer better health services, whilst more stable patients may have attended primary care clinics. Such patients with advanced disease are more likely to die and may have been masked as LFTU patients. In a systematic review of studies tracing ART patients lost to follow-up in resource-limited settings, mortality was shown to range from 20% to as high as 60%.[31]

In contrast to previous studies,[37] the baseline CD4 cell count was not associated with attrition for both males and females. This could be explained in part by the amount of missing baseline CD4 count data, which exceeded 50% for the abstracted patient records, although this missing information was variable among sampled patient records and did not constitute any specific subgroup of patients. Our study did not assess self-reported ART interruptions or adherence, which may be linked to ART attrition. In a Cameroonian study by Marcellin et al.,[38] pharmacy stock shortages, binge drinking, and the number of self-reported slimming symptoms were associated with ART interruptions, and food supply programs were suggested as interventions to limit these ART interruptions.

Other study limitations include missing data on haemoglobin measurements, and given that nearly three-quarters of those with documented haemoglobin measurements were anaemic, could suggest that these measurements were taken in those suspected of having anaemia. Data were also unavailable for patient height and thus we were unable to calculate body mass index (BMI). Whilst it may have been ideal to determine actual patient outcomes of all patients, we could not trace and establish true patient outcomes in those patients who were classified as LTFU and there is a possibility that some may have been alive or dead and thus misclassified. This potential misclassification of ART patients in the attrition group is not uncommon in retrospective reviews of other ART patient cohorts in other resource-limited settings.

In conclusion, our study findings show that males present late for ART when compared with their female counterparts. This may partly explain their poorer outcomes in comparison to females. This observation highlights the need for strategies tailored to males in order to encourage early HIV testing and enrolment into HIV treatment and care.

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